# IS CARDIOPULMONARY BYPASS STILL THE CAUSE OF COGNITIVE DYSFUNCTION AFTER CARDIAC OPERATIONS?

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***Objective:*** **The purpose of this study was to determine whether cognitive impairment is related to cardiopulmonary bypass.** ***Methods:*** **Twenty-five patients undergoing coronary artery bypass grafting without cardiopulmonary bypass were matched with 50 patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. All patients received the same anesthetic regimen, and one surgeon performed all the operations. A battery of 10 standard tests of neuropsychologic function were performed before, at discharge, and 3 months after the operation. A comprehensive multidimensional measure of subjective health status was used as the primary clinical measure of functional outcome.** ***Results:*** **The groups were similar with respect to age, sex, and ventricular function and differed only in the need for a circumflex artery graft. Both groups showed significant improvement in the comprehensive multidimensional measure of subjective health status at 3 months. At discharge most neuropsychologic tests had deteriorated in both groups (the same 4 tests had deteriorated significantly in both groups, and an additional test had deteriorated significantly in the cardiopulmonary bypass group). At 3 months all but one test in the cardiopulmonary bypass group had returned to or exceeded baseline performance. The same 2 tests had improved significantly in both groups, and a further test had improved significantly in the group without cardiopulmonary bypass. At no specific time point was there a significant difference between the absolute or change scores between the groups on any of the tests.** ***Conclusions:*** **The similar pattern of early decline and late recovery of cognitive function in patients undergoing coronary artery bypass grafting with and without cardiopulmonary bypass suggests that cardiopulmonary bypass is not the major cause of postoperative cognitive impairment. This merits consideration in deciding optimal treatment strategies in coronary revascularization. (J Thorac Cardiovasc Surg 1999;118:414-21)**

Advances in the protection of the heart and other organs during cardiac operation leaves acute cerebral injury as the major limitation.[1] Cerebral injury occurs in 2 forms after cardiac operation: a clinically obvious deficit occurs in 3% of patients and is attributed to embolization of atherosclerotic debris during manipulation of the diseased aorta; cognitive impairment occurs in two thirds of patients early after operation and, more importantly, is reported to persist in one third of patients for at least 1 year after operation. The precise pathophysiologic features of cognitive impairment are not certain but have been attributed to the microembolic, inflammatory, and nonphysiologic perfusion factors associated with cardiopulmonary bypass (CPB).[2]

Cognitive impairment also occurs after noncardiac operations but is reported to be more frequent and severe after cardiac operation with CPB.[3-9] Although cognitive impairment after noncardiac operation is

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explained by patient-related factors (eg, advanced age, ill health), impairment that occurs after cardiac operation is invariably attributed to CPB.[3-9]

The feasibility of the performance of certain coronary grafts without CPB has recently been established. Grafts to the left anterior descending and right coronary artery can be performed with minimal disturbance of the heart and the avoidance of CPB; grafts to the circumflex artery require significant manipulation of the heart and CPB to support the circulation. It has been postulated, but not proved, that avoidance of CPB may reduce the postoperative morbidity associated with extracorporeal circulation. Specifically, it is suggested that coronary artery bypass grafting (CABG) without CPB should minimize postoperative cognitive impairment. Testing this hypothesis ideally requires a randomized trial of patients undergoing CABG with and without CPB.

To investigate the current impact of CPB on cognitive functioning, we compared neuropsychologic performance at discharge and at 3 months in patients undergoing CABG with and without CPB. Furthermore, functional performance as measured by the comprehensive multidimensional measure of subjective health status (SF36) was compared before and 3 months after the operation. The SF36 is a generic measure of subjective health status that assesses daily function covering physical and social function, emotional problems, bodily pain, vitality, and health perceptions.[10] We hypothesized that if CPB is the cause of neuropsychologic impairment over and above other intraoperative factors then patients undergoing CABG without CPB would be expected to show better psychometric performance than those patients undergoing CABG with CPB.

## Methods

**Patients.** The 50 patients with CPB in the current study were from a group of 150 patients undergoing CPB and were taking part in a trial, “A Phase 2 Study Assessing the Effect of a 12 Hour Infusion of Lexipifant on Myocardial Damage, Lung Injury, and Cerebral Dysfunction in Patients Undergoing Coronary Artery Bypass Grafting” between February 1996 and March 1997. This trial was approved by the Central Oxford Research Ethics Committee (“95.280”). All patients gave written informed consent to participate in this trial. The patients undergoing nonbypass studies gave consent to follow the same protocol as the patients in the cardiopulmonary trial. This study did not require ethical committee approval because it did not involve randomization of patients and did not involve invasive measurements. The inclusion criteria for that study included patients undergoing first-time CABG for angiographically demonstrated coronary stenoses. Exclusion criteria included emergency operation, significantly impaired ventricular function (ejection fraction < 30%), or a previous cerebrovascular accident.

The 25 patients undergoing CABG without CPB were from a group of 26 such patients who underwent operation consecutively between March 1996 and February 1997. One patient who underwent an emergency operation was not included in neuropsychologic testing. The patients without CPB were defined solely by the absence of circumflex coronary artery disease on preoperative coronary angiography and otherwise met all criteria to be entered into the anti-inflammatory trial. Each patient without CPB was matched with 2 patients with CPB in terms of age and sex. As a consequence of this a priori matching, the groups were also found to be closely matched for pre-existing hypertension and ventricular function. These factors (except sex) may influence, albeit weakly, postoperative neuropsychologic outcome.[2,9]

**Anesthesia.** The patients with CPB and without CPB received the same anesthetic regimen. Premedication was achieved with morphine (10-15 mg) and scopolamine (0.3-0.4 mg). Anesthesia was induced with fentanyl (1 mg), pancuronium (8 mg), and etomidate (4-10 mg). Anesthesia was maintained with a combination of oxygen, nitrous oxide, and halothane before CPB and during CPB with propofol (6 mg/kg per hour). Benzodiazepines were not used.

**Operation.** One surgeon (D.P.T.) performed all operations through a median sternotomy incision. CABG without CPB was performed in patients whose condition required grafts to any coronary vessels, excluding the circumflex marginal or its branches. These patients received half-dose heparin, and the heart was displaced medially with a swab placed in the left side of the pericardium. This usually reduced the mean arterial pressure to 50 to 60 mm Hg, but if necessary a short-acting β-blocker was added to reduce blood pressure to this level. Stay sutures placed proximal and distal to the intended site of anastomosis secured the coronary artery. Proximal anastomoses, where relevant, were constructed with a side-biting clamp occluding a palpably normal portion of ascending aorta.

**CPB.** CPB was achieved with a pump flow rate of 2.4 L/m$^2$ per minute at normothermia with temperature allowed to drift to 34°C. Topical cooling was not used, and there was no direct or indirect left ventricular venting. A membrane oxygenator (Cobe CML; Cobe Cardiovascular, Inc, Quedgeley, Gloucester, United Kingdom) and a roller pump that produced nonpulsatile flow were used without an arterial line filter. Alpha-stat control of acid-base management was used, and the mean arterial pressure was maintained between 50 and 60 mm Hg with pharmacologic manipulation if necessary. Distal anastomoses were constructed during brief periods (approximately 10 minutes) of aortic clamping and induced fibrillation. Proximal anastomoses were constructed with a side-biting clamp.

**Neuropsychologic and functional assessment.** All patients underwent neuropsychologic tests and a comprehensive multidimensional measure of subjective health status (SF36). One examiner (S.M.B.) administered a battery of 10 standardized neuropsychologic tests before the operation, before discharge, and 3 months after the operation. The examiner, who was responsible for recruitment of patients into the anti-inflammatory study, was therefore not blinded to

**Table I.** *Patient characteristics**

| | CPB (n = 50) | Without CPB (n = 25) | P value |
|---|---|---|---|
| Age (y) | 58.9 ± 10.4 | 59.2 ± 10.2 | .95 |
| IQ estimate (NART) | 108.8 ± 9.3 | 108.1 ± 8.5 | .7 |
| Sex (% male) | 88 | 88 | 1.0 |
| Elective (%) | 70 | 56 | .23 |
| Hypertension (%) | 38 | 40 | .87 |
| Diabetes (%) | 16 | 20 | .67 |
| LV function (% normal) | 74 | 84 | .33 |
| Grafts (mean) | 2.7 ± 0.5 | 1.5 ± 0.5 | .0001 |
| Grafts (n) | | | |
| 1 | 0 | 13 | |
| 2 | 14 | 12 | |
| 3 | 35 | 0 | |
| 4 | 1 | 0 | |
| Operation time (min) | 175 ± 46 | 126 ± 59 | .0001 |
| CPB duration (min) | 68 ± 18 | — | |
| Length of hospital stay (d) | 6.2 ± 1.8 | 6.3 ± 2.1 | .98 |

*IQ*, Intelligence quotient; *NART*, National Adult Reading Test.
*Data given as mean and SD, unless otherwise indicated.

patients in the group without CPB. The tests are described in detail elsewhere[11] but included tests from a battery recommended by a consensus conference on the assessment of neurobehavioral outcomes after cardiac operations.[12] The tests examine the following cognitive domains: premorbid intelligence (National Adult Reading Test); verbal memory (Rey Auditory Verbal Memory Test); attention (Digit span: forward and backward, Trail-Making Tests A and B); psychomotor speed (Nine Hole Pegboard Test); verbal performance (verbal fluency); visual search (Bells test); speed of information processing (Adult Memory Information Battery: Test A), and general cognitive orientation (Short Orientation Memory Concentration Test). To ascertain whether the neuropsychologic deficits had an impact on daily functioning, preoperative scores on the subjective health status measure (SF36) were also compared with 3-month performance.

**Statistical analysis.** Statistical analysis was undertaken with the SPSS pc (version 6.1) computer program. Within subject changes (between preoperative and discharge scores and between preoperative and 3-month scores) were analyzed separately with paired *t* tests. Between-group differences were analyzed with independent *t* tests and 95% confidence intervals (CIs; based on the calculated change scores). Patient characteristics data (Table I) were analyzed with the $\chi^2$ test (for categoric data) and the Mann-Whitney test (for continuous data). Change scores for the trail-making test B were calculated after the transformation of the raw scores to natural log values, because the distribution of the raw change scores were not normal. To minimize the impact of nonrandomization, we performed multiple regression analyses on baseline variables.

## Results

The 50 patients with CPB were drawn from an anti-inflammatory study that showed no significant difference in neuropsychologic performance between the active and placebo groups. Mann-Whitney tests on all relevant data at all 3 time points showed no significant difference in any neuropsychologic test at any time point between the 50 patients drawn from the anti-inflammatory study and the remainder of the patients in that study.

Patient demographics of the current study are summarized in Table I. The groups were similar with respect to age, sex, pre-existing hypertension, and ventricular function. The number of grafts was significantly higher in the CPB group with a mean ± standard deviation (SD) of 2.7 ± 0.5 versus a mean of 1.5 ± 0.5 in the group without CPB. The operation times were significantly different; the operation time for the group without CPB was approximately 50 minutes shorter than that for the group with CPB. The conditions of patients in both groups were managed by the standard unit policy of early extubation. Postoperative length of stay was similar in the 2 groups, although patients who would have been suitable for discharge at an earlier date were requested to stay in the hospital for completion of neuropsychologic testing.

Tables II and III show the mean (SD) scores for each test in both groups before operation and 5 days after operation (Table II) and 3 months after operation (Table III). The tables show the mean and 95% CI difference within each group and the mean and 95% CI difference between the change scores in both groups at 5 days (Table II) and at 3 months (Table III).

At discharge most neuropsychologic tests had deteriorated in both groups. In both groups the same 4 tests had deteriorated significantly (speed of information processing, right- and left-hand pegboard test, and visual search) with a significant deterioration in one other test in the CPB group (delayed recall). At 3 months all but one test result (visual search in the CPB group) had returned to or exceeded baseline performance. The same 2 tests had improved significantly in both groups (speed of information processing and left-hand pegboard test), and additionally the right-hand pegboard test in the group without CPB. At no specific time point was there a significant difference between the absolute or change scores between the groups on any of the tests.

The SF36 was completed by 46 patients with CPB and all patients without CPB. Both groups showed significant mean improvement in the physical functioning component at 3 months. The CPB group increased from 48 (25) to 70 (26) [mean improvement, 22; 95% CI, 15%-30%: $P < .0005$] and the group without CPB increased from 40 (29) to 63 (25) [mean improvement, 23; 95% CI, 11%-35%; $P < .001$]. Both groups also

**Table II.** *Mean (± SD) neuropsychologic test performance, comparing preoperative and discharge scores (5 days) for patients with and without CPB*

| *Test* | *Group* | *N* | *Preoperative mean* | *Discharge mean* | *Difference within groups (95% CI)* | P *value* | *Difference between the mean change score for both groups (95% CI)* | P *value CPB vs without CPB* |
|---|---|---|---|---|---|---|---|---|
| Immediate recall | CPB | 49 | 40.6 (7.9) | 40.1 (8.2) | –0.6 (–2.2/+1.1) | .51 | –2.0 (–1.3/+5.3) | .22 |
| | Without CPB | 23 | 42.4 (9.7) | 39.9 (10.6) | –2.6 (–5.9/+0.7) | .12 | | |
| Delayed recall | CPB | 49 | 15.0 (5.8) | 12.6 (5.5) | –2.4 (–3.6/–1.1) | .0001 | –1.2 (–3.1/+2.8) | .89 |
| | Without CPB | 22 | 16.2 (5.9) | 14.0 (5.9) | –2.2 (–4.9/+0.5) | .11 | | |
| Speed of information processing | CPB | 49 | 66.1 (16.1) | 58.7 (17.4) | –7.1 (–9.9/–5.0) | .0001 | –3.4 (–7.6/+0.9) | .12 |
| | Without CPB | 23 | 61.8 (16.9) | 57.7 (18.2) | –4.1 (–7.7/–0.5) | .03 | | |
| Trail making, test A* | CPB | 50 | 36.6 (13.4) | 38.5 (13.8) | –1.9 (–4.2/+0.3) | .09 | 1.0 (–3.3/+5.3) | .65 |
| | Without CPB | 23 | 33.7 (9.7) | 36.6 (14.4) | –3.0 (–7.3/+1.4) | .17 | | |
| Trail making, test B* | CPB | 47 | 91.2 (33.7) | 122.3 (73.6) | –31.1 (NA) | — | 7.1 (–22.3/+36.4) | .61 |
| | Without CPB | 23 | 94.3 (31.4) | 132.4 (90.1) | –38.2 (NA) | — | | |
| Pegboard, right hand* | CPB | 49 | 18.9 (2.2) | 20.8 (2.7) | –1.9 (–2.4/–1.5) | .0001 | –0.7 (–1.9/+0.7) | .32 |
| | Without CPB | 23 | 19.5 (2.9) | 20.7 (3.1) | –1.3 (–2.5/0) | .05 | | |
| Pegboard, left hand* | CPB | 49 | 20.8 (3.5) | 22.4 (4.1) | –1.6 (–2.4/–0.8) | .0001 | –0.6 (–1.9/+0.7) | .38 |
| | Without CPB | 22 | 21.1 (3.2) | 22.2 (3.9) | –1.0 (–1.9/–0.2) | .02 | | |
| Verbal fluency | CPB | 49 | 38.2 (12.8) | 37.2 (12.1) | –1.0 (–3.1/+1.0) | .32 | –1.06 (–4.9/+2.8) | .59 |
| | Without CPB | 22 | 39.0 (12.5) | 39.1 (12.0) | +0.1 (–3.8/+3.9) | .98 | | |
| Digit span (forward) | CPB | 49 | 6.4 (1.2) | 6.3 (1.3) | –0.1 (–0.5/+0.2) | .4 | –0.4 (–0.9/+0.2) | .16 |
| | Without CPB | 23 | 6.0 (1.3) | 6.3 (1.4) | +0.3 (–0.2/+0.2) | .21 | | |
| Digit span (backward) | CPB | 49 | 4.9 (1.3) | 4.7 (1.5) | –0.2 (–0.5/+0.1) | .12 | –0.4 (–0.9/+0.1) | .13 |
| | Without CPB | 23 | 4.6 (1.2) | 4.7 (1.3) | +0.1 (–0.2/+0.7) | .48 | | |
| Visual search | CPB | 49 | 2.2 (2.2) | 1.6 (1.6) | +0.6 (–0.1/+1.3) | .09 | –0.2 (–1.4/+1.0) | .78 |
| | Without CPB | 23 | 1.9 (2.1) | 1.2 (1.7) | +0.8 (–0.1/+1.7) | .09 | | |
| SOMCT | CPB | 50 | 25.2 (2.4) | 24.9 (3.1) | –0.3 (–1.1/+0.5) | .42 | –0.5 (–20/+1.0) | .51 |
| | Without CPB | 23 | 25.1 (2.7) | 25.3 (3.2) | +0.2 (–1.3/1.7) | .81 | | |

*SOMCT*, Short Orientation Memory Concentration Test.
Slight discrepancies in results are due to rounding up/down of decimal figures. On most tests, a higher score represents better performance. Tests marked with an asterisk (*) used time measurement; consequently, higher scores represent poorer performance. Raw scores are used for Trail Making Tests A and B. In the case of Trail Making Test B, all preoperative scores of more than 200 seconds were excluded from analysis, and all noncompleted tests were assigned a time of 331 seconds (equal to the largest completed time). Given the distribution of change scores for Trail Making Test B, the Mann-Whitney *U* test was used.

showed significant improvement in the sociomental component of the SF36. The CPB group increased from 59 (21) to 75 (19) [mean improvement, 16; 95% CI, 11%-21%; $P < .0005$] and the group without CPB increased from 50 (25) to 73 (21) [mean improvement, 23; 95% CI, 16%-30%; $P < .0005$]. The mean differences between the change scores of each surgical group at 3 months for each component of the SF36 were not significant (physical: mean difference, –1; 95% CI, –14%-13%; $P = .91$; sociomental: mean difference, –7; 95% CI, –15%-2%; $P = .11$).

Because change scores can be biased by baseline imbalance, particularly in nonrandomized studies, multiple regression equations were calculated with the discharge and 3-month scores as the dependent variables and the preoperative scores and the CPB group (assigned dummy scores) as the independent variables. This was done for each test at each time point, and on no occasion did CPB become a significant independent variable. In other words, by controlling for the preoperative score, the presence or absence of CPB made no difference to the dependent scores.

## Discussion

Before a discussion of the results of this study can occur, it is important to consider the design and limitations. We had already embarked on a trial of an anti-inflammatory agent in a group of 150 patients undergoing conventional CABG with CPB when the technical feasibility of CABG without CPB for certain patients was described.

The patients without CPB were defined only by the absence of circumflex coronary artery and met all the criteria to be entered into the anti-inflammatory trial. Because less than 2% of our CABG population are potentially suitable for revascularization without CPB, it was not practical, given the time frame, to randomize these patients between CPB and without CPB. The patients without CPB were, in effect, selectively withdrawn from the anti-inflammatory trial but followed

**Table III.** *Mean (± SD) neuropsychologic test performance comparing preoperative and 3-month scores for patients with and without CPB*

| *Test* | *Group* | *N* | *Preoperative mean* | *Discharge mean* | *Difference within groups (95% CI)* | P *value* | *Difference between the mean change score for both groups (95% CI)* | P *value CPB vs without CPB* |
|---|---|---|---|---|---|---|---|---|
| Immediate recall | CPB | 50 | 40.3 (8.2) | 40.8 (9.1) | +0.5 (–1.2/+2.3) | .53 | 0.2 (–2.7/+3.1) | .9 |
| | Without CPB | 25 | 42.6 (9.6) | 42.9 (9.1) | +0.4(–2.0/+2.7) | .76 | | |
| Delayed recall | CPB | 50 | 14.8 (6.0) | 13.7 (6.2) | –1.0 (–2.2/+0.2) | .09 | 0.0 (–2.2/+2.1) | .99 |
| | Without CPB | 25 | 16.4 (5.7) | 15.4 (6.4) | –1.0 (–2.9/+0.9) | .30 | | |
| Speed of information processing | CPB | 50 | 65.7 (16.2) | 68.5 (18.3) | +2.8 (+0.4/+5.1) | .02 | –2.7 (–6.4/+1.1) | .16 |
| | Without CPB | 25 | 63.1 (16.9) | 68.6 (18.7) | +5.4 (+2.9/+7.9) | .001 | | |
| Trail Making Test A* | CPB | 50 | 36.6 (13.4) | 34.1 (9.9) | +2.5 (–0.6/+5.5) | .11 | 0.6 (–4.1/+5.3) | .79 |
| | Without CPB | 25 | 33.0 (9.5) | 31.2 (10.9) | +1.8 (–0.9/+4.7) | .19 | | |
| Trail Making Test B* | CPB | 47 | 91.2 (33.7) | 88.2 (45.1) | +3.0 (NA) | — | –0.6 (–17.1/+15.9) | .98 |
| | Without CPB | 25 | 92.2 (31.3) | 88.6 (33.8) | +3.6 (NA) | — | | |
| Pegboard, right hand* | CPB | 50 | 18.8 (2.2) | 18.4 (2.1) | +0.4 (–0.1/+0.9) | .08 | –0.5 (–1.5/+0.5) | .32 |
| | Without CPB | 25 | 19.3 (2.9) | 18.4 (2.5) | +0.9 (0.0/+1.8) | .04 | | |
| Pegboard, left hand* | CPB | 50 | 20.8 (3.4) | 19.8 (3.1) | +1.0 (+0.3/+1.7) | .004 | –0.30 (–1.4/+0.8) | .62 |
| | Without CPB | 24 | 21.0 (3.1) | 19.7 (2.9) | +1.3 (+0.4/+2.1) | .004 | | |
| Verbal fluency | CPB | 50 | 37.9 (12.8) | 38.6 (12.3) | +0.7 (–1.7/+3.0) | .57 | –0.1 (–3.8/+3.7) | .97 |
| | Without CPB | 25 | 39.1 (12.3) | 39.8 (10.9) | +0.7 (–1.9/+3.3) | .57 | | |
| Digit span (forward) | CPB | 50 | 6.4 (1.3) | 6.6 (1.3) | +0.2 (–0.1/+0.2) | .14 | –0.3 (–0.8/+0.3) | .33 |
| | Without CPB | 25 | 6.0 (1.3) | 6.5 (1.2) | +0.5 (0.0/+0.9) | .06 | | |
| Digit span (backward) | CPB | 50 | 4.9 (1.3) | 4.9 (1.5) | +0.1 (–0.2/+0.4) | .58 | –0.1 (–0.6/+0.4) | .63 |
| | Without CPB | 25 | 4.6 (1.1) | 4.8 (1.3) | +0.2 (–0.2/+0.6) | .33 | | |
| Visual search | CPB | 50 | 2.2 (2.2) | 1.3 (1.3) | +0.9 (+0.4/+1.5) | .002 | 0.7 (0.3/+1.7) | .19 |
| | Without CPB | 25 | 1.9 (2.0) | 1.7 (1.6) | +0.2 (–0.7/+1.2) | .60 | | |
| SOMCT | CPB | 50 | 25.2 (2.4) | 25.5 (3.3) | +0.3 (–0.6/+1.2) | .52 | –0.2 (–1.6/+1.2) | .78 |
| | Without CPB | 25 | 24.9 (2.7) | 24.4 (2.4) | +05 (–0.6/+1.6) | .37 | | |

*SOMCT*, Short Orientation Memory Concentration Test. Slight discrepancies in results are due to rounding up/down of decimal figures. On most tests, a higher score represents better performance. Tests marked with an asterisk (*) used time measurement; consequently, higher scores represent poorer performance. Raw scores are used for Trail Making Tests A and B. In the case of Trail B, all preoperative scores of more than 200 seconds were excluded from analysis, and all noncompleted tests were assigned a time of 331 seconds (equal to the largest completed time). Given the distribution of change scores for Trail Making Test B, the Mann-Whitney *U* test was used.

the same assessment protocol, because the postulated benefits of avoiding CPB have not yet been established.

The 50 patients with CPB were drawn from an anti-inflammatory drug trial that showed no difference in postoperative cognitive function between the active and placebo groups. These 50 patients showed no significant difference in any neuropsychologic test at any time point from the remainder of the patients in that study. Although we did not randomize the current study, the groups were matched for age, sex, pre-existing hypertension, and ventricular function. Advanced age (>70 years) and severe impairment of ventricular function (ejection fraction < 30%) may influence, albeit weakly, postoperative cognitive function.[2,9] The mean age of patients in our study was less than 60 years, and patients with significantly impaired ventricular function were excluded. Furthermore, multiple regression analysis showed that minor differences in preoperative variables did not influence our results.

A potential weakness of our study was that the neuropsychologic tests were performed by one observer who was not blinded to the groups with and without CPB. In addition to the fact that many of the neuropsychologic tests are objective and quantifiable assessments of cognitive performance and not easily influenced by the examiner, our postulated a priori bias was that the group without CPB would perform better than the group with CPB by avoiding CPB. That the patients without CPB also had less severe coronary artery disease (suggesting the possibility of less widespread arterial disease) and shorter operating times was expected to support this postulate.

On the multidimensional health questionnaire (SF36), both groups showed a similar significant improvement at 3 months. The more surprising observation in our study was the similarity of cognitive impairment at discharge and the lack of difference in cognitive performance at 3 months. Considering that the group without CPB also had less severe coronary artery disease and shorter operating times makes our observations even more striking. At discharge most tests were impaired in comparison with preoperative baseline in both groups: at 3 months, all but a single test in the CPB group had returned to or exceeded baseline performance. Although the absence of improvement in any test on repeated examination might itself represent some degree of impairment, this should apply to both groups and therefore would not invalidate the comparison between the groups.

Cognitive dysfunction has been reported to persist for several months or even years after CABG. The return to baseline scores for most tests in our CPB group at 3 months is, however, in keeping with data from recent studies that report significant improvements in cognitive function late after cardiac operations[17,18] and the clinical impression that cognitive impairment is now uncommon late after cardiac operations. This reduction in late cognitive impairment is probably due to refinements in extracorporeal circulation including the use of arterial line filters[13] and membrane oxygenators[14,15] and improved control of acid-base balance.[16]

Our results are also consistent with earlier studies that suggested that CBP was not the sole cause of cerebral dysfunction after cardiac operations.[3-9] Our findings confirm and extend the recent study of Malheiros and colleagues,[19] who reported no difference in neurologic or neuropsychologic outcome on postoperative day 7 in patients undergoing CABG with or without CPB.

Collectively, these studies question the established dogma that CPB is responsible for cognitive impairment after cardiac operations, at least in patients undergoing closed operations and with at least moderate ventricular function. If, however, CPB is not specifically responsible for cognitive impairment at early and late follow-up, what alternative intraoperative components common to both operations could be involved? Several candidates present themselves that include hypotension, general surgical injury, and anesthesia.

Although severe intraoperative hypotension may cause cognitive dysfunction, most prospective studies have failed to confirm this when mean arterial pressure is maintained above 50 mm Hg,[20-24] a level at which cerebral autoregulation normally occurs. In our study the mean blood pressure was maintained at 50 to 60 mm Hg in both groups.

The contribution of the general effects of surgical injury warrants consideration, given previous findings that patients undergoing major noncardiac operation also showed cognitive dysfunction.[3-9] These studies cannot, however, distinguish the effects of surgical injury from those of concomitant anesthesia. To resolve this issue would require submitting age-matched patients to the same anesthetic regimen but without operation, not an ethical proposition.

Could the pattern of neuropsychologic impairment after CABG, with or without CPB, and other forms of operation be explained in terms of the effects of the anesthetic regimen? Although it is generally recognized that anesthesia can produce short-term cognitive dysfunction,[25,26] the long-term effects remain open to question.[27,28] Furthermore, when evaluating the effects of anesthesia, most studies typically consider only the effects of a single agent. Few, if any, consider the potential for the cumulative and/or interactive effects of different agents commonly used.[29] As emphasized by Klafta and colleagues,[27] however, the typical anesthetic regimen for cardiac operations produces “deeper anaesthesia than is normally required for non-cardiac operation.”

In the largest trial to date that investigated the effects of general and epidural anesthesia in orthopedic patients, 5% of all patients showed clinically significant deterioration on a large battery of neuropsychologic tests at 6 months.[28] Furthermore, 27% of all patients showed a clinically important deterioration in verbal memory at 6 months. The authors speculate that this cognitive dysfunction might result from anesthetic-dependent cerebral ischemia or disturbances of cerebral autoregulation.[28] Taken together, these studies suggest it is pertinent to re-examine the role of polypharmacy of particular anesthetic regimens when considering postoperative cognitive dysfunction.

Although our results confirm previous reports of an early deterioration in neuropsychologic function after cardiac operations, they clearly imply that this is not exclusive to the use of CPB. Avoidance of cerebral dysfunction has been used as a major reason for promoting minimally invasive operations over conventional CABG with CPB despite inferior long-term results. Our results, however, suggest that the particular anesthetic regimen in association with nonspecific effects of the general operation may be responsible for producing the common pattern of cognitive dysfunction after cardiac operations. This merits further investigation.

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## Commentary

In this provocative study, Taggart and colleagues have apparently been unable to demonstrate any meaningful differences in postoperative cognitive outcomes in patients undergoing coronary revascularization with or without the use of cardiopulmonary bypass (CPB). Although there may be some significant methodologic points at issue relating to the detection of cognitive dysfunction and revolving around the use of group mean analysis, as used here, versus incidence analysis, as has been recommended elsewhere,[1] the clinical message appears to be that there are no meaningful differences in cognitive outcomes irrespective of whether or not CPB is used. Before this result is uncritically accepted and generalized, however, careful consideration must be given to the specific conditions of this study.

In the first instance, this study was not randomized. The 50 patients comprising the CPB group were in fact drawn as a subset from 150 patients undergoing a separate, randomized controlled trial of an anti-inflammatory agent. Since this group was matched post hoc for age and sex with the 25 patients in whom CPB was not used (no CPB), and necessarily included only those patients with complete data sets, CPB patients with significant complications (eg, mortality, stroke, important hemodynamic complications) or those lost to follow-up would not have been represented in the CPB comparison group. This fact alone raises the possibility of significant inadvertent bias in favor of the CPB group.

Irrespective of this confound, however, the fact remains that for these selected groups these data, as analyzed, do not appear to show any meaningful differences in outcome ascribable to use of CPB. What else is different about these groups? Certainly the average age of the 2 study groups is considerably younger than that for those undergoing surgical coronary revascularization in North America. On the basis of the latest figures available from The Society of Thoracic Surgeons Adult Cardiac National Database, the average age of patients undergoing coronary artery bypass grafting (CABG) in North America in 1996 was 64.7 ± 10.6 years.[2] This is in contrast to the mean age of 58.9 ± 10 years in the current study. Is this germane? The risks of neurologic and cognitive injury after CPB are largely determined by age. In a prospective study of 2108 patients undergoing CABG, 32% of patients were aged 70 years or older, and older age was shown to be a significant independent risk factor for both stroke (type I) and deterioration of intellectual function (type II) outcomes.[3] Others have also shown a specific association between age and postoperative cognitive dysfunction in patients undergoing conventional CABG.[4] Given that the proportion of CABG patients older than 70 years exceeds 30% in most clinical practices in North America, before determining operative strategy on the basis of the results of the current study, we must be fully aware that although these results may apply, they may well apply only to those patients younger than 60 years.

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